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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/777,849	CHACKALAMANNIL ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Withdrawal from issue*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,22-35,37 and 39-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,22-35,37 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The allowance of this application is withdrawn; prosecution is reopened.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The list of claim 31 is supposed to be a "disorder, symptom or disease". However, endarterectomy and stent introduction are neither; these are procedures. It is unclear whether applicants intend conditions that would necessitate e.g. endarterectomy, or conditions caused by endarterectomy, or perhaps something else.

B. Similarly, "intestinal motility" is not a disease, etc., but just a measure of how fast food moves through the GI tract.

C. The term "Diabetes" is ambiguous. It is not a complete term. Diabetes insipidus for example is caused by the inability of the kidneys to conserve water, which is caused by a lack of ADH (central diabetes insipidus) or by failure of the kidneys to respond to ADH (nephrogenic diabetes insipidus). Applicants must select some specific form(s) of diabetes

(e.g. Type 2 diabetes mellitus, or Gestational diabetes mellitus; these are metabolic disorders) and they must use that term, and show that one of ordinary skill in the art would have been able to determine that whatever term(s) is/are selected was the one(s) intended.

D. The term "tubular interstitial" is fragmentary. Is tubular interstitial fibrosis or tubular interstitial scarring or tubular interstitial lesions or what intended?

Claims 1-12, 24-35, 37, 39-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The Y choice of $-(R^{23})(R^{24})N(H)-$ (second from last line of page 4) is clearly defective, as it provides for a N atom with 5 bonds, which is impossible. For whichever choice is made, applicants must show that one of ordinary skill in the art would have known that this choice, and not another, was intended.
2. The structures with R25 and R26 on them for Y are defective, as the bonds are attached to the H rather than the C.
3. "Thioalkyl", which occurs in the definition of the substituents on page 6 and elsewhere, is not standard nomenclature. Thio as a generic prefix simply indicating the presence of sulfur. It could have a number of possible meanings. It is possible that the term refers to HS-alkyl-, which is properly called the mercaptoalkyl group. It is also possible that it is intended to refer to the alkyl-S- group, which is properly called the alkylthio group. It could possibly refer to the replacement of a carbon in an alkyl with a Sulfur, e.g. CH_3-S-CH_2-. Another alternative is that the sulfur could be a double bonded substituent (rather than a single bonded one as seen in mercaptoalkyl), e.g. CH_3-C(=S)-CH_2-,

properly called the thioxo alkyl. There might be some letters missing, so that what was intended was thiophenylalkyl, i.e. the alkyl is substituted by thiophene, or possibly thionoalkyl, i.e. alkyl substituted by =C=S. This specification gives no clear evidence as to which of these plausible choices was originally intended.

4. When R50 and R51 are combined to form a ring, these much be combined with the atom wo which these are attached. Likewise the ring from R61-R62, etc.
5. What is the purpose of the structures on page 7? These are already covered by the first part of the definition, are they not?
6. The limitations of claims 24-27 are unclear. The values depend of the procedure involved, e.g. the source of the PDE5 (human? Porcine?), the specific incubation and buffering procedures, etc. Different procedures will give different values.
7. The term "ester" (see e.g. R9, R10 in claim 27) is not a substituent, but a compound, e.g. ethyl acetate. As such, it has no valence and cannot be a substituent.
8. The claim 27 formula is problematic. If the material in parenthesis is correct, then n and m can only be 2 (i.e. the material in parenthesis is –CH=CH-). Note that carbon must have 4 bonds. If e.g. m=3, then two carbons will be taken care of with –CH=CH- but the third will have only three bonds. Moreover, this conflicts with the requirement that the ring must be saturated, as is stated on page 12, line 7 of the specification.
9. In the R10-R11 combined option (page 13), , the "optionally" is wrong. The ring must include at least one atom from the ring.
10. Further the "and/or heteroatoms" is not quite right. The "or" part is wrong. R10 and R11 cannot be both attached to just a heteroatom – no heteroatom has 2 hydrogens to replace.

Claim 40 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In the first step (i) of claim 40, (III) is reacted with an "alkyl halide" to introduce the L group. The problem is, L is R2, but R2 can be far more than alkyl. R2 can be for example aryl (see claim 6) or heteroaryl, etc. Thus, either the "alkyl halide" reagent is wrong, or the wrong definition is used for L or for R2.

B. The same occurs in step (ii), where step 2 is an aralkylation, not an alkylation, since R3 is defined as aryl.

Claims 31-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Owing to the vast scope of the four primary variables, the claims cover trillions of compounds.

(b) Scope of the diseases covered. The coverage of claim 31 is immense. Some aspects of the claim:

A. Cancer. There are hundreds of types of cancers and tumors. They can occur in pretty much every part of the body.

B. Cardiovascular and cerebrovascular disorders embraces a vast array of problems, some of which are contradictory to others. This covers various forms of endocarditis, including Verrucous, Atypical verrucous (Libman-Sacks) Non-bacterial thrombotic - NBTE (marantic), bacterial, viral, and rickettsial endocarditis. It covers different forms of atresia, including tricuspid atresia without TGV, pulmonic valvular atresia and aortic atresia. It includes assorted cardiomyopathies, including restrictive cardiomyopathy, peripartum cardiomyopathy, hypertrophic cardiomyopathy, and congenital cardiomyopathy. It embraces various forms of aortic Stenosis, including valvular aortic Stenosis, idiopathic hypertrophic sub-aortic stenosis (IHSS), subvalvular aortic stenosis, and supravalvular aortic stenosis. There are all kinds of miscellaneous syndromes, including subclavian steal syndrome, Eisenmenger syndrome, mitral valve prolapse (Barlow) syndrome, Aortic arch syndrome, scimitar syndrome, hypoplastic left heart syndrome, Lutembacher syndrome, and superior vena cava syndrome. It covers various forms of hypertension, including primary (idiopathic) pulmonary hypertension, neonatal pulmonary venous hypertension and pulmonary hypertension. It includes aortic aneurysms, including both thoracic and abdominal, as well as mycotic aneurysm. It covers various types of arrhythmias and atrial fibrillation. It covers elevated blood levels of

triglycerides, of total cholesterol or of LDL cholesterol, and hyperlipoproteinaemias. It covers different forms of ischaemic heart disease including congestive heart failure and myocardial infarction. It covers a vast array of structural defects such as atrial septal defect (ASD), aorticopulmonary window, egg-on-its-side heart, gooseneck deformity, endocardial cushion defect, arc of Buehler, arc of Riolan, truncus arteriosus, Ebstein's Malformation, azygos continuation of interrupted IVC, Atrioventricular Canal, ventricular septal defect (VSD), abdominal aortic coarctation, aortic pseudo-coarctation, complete endocardial cushion defect, Hypoplastic Left Heart, patent ductus arteriosus (PDA), congenital absence of pulmonary valve, aortic coarctation partial endocardial cushion defect, Single Ventricle, box-like heart, pulmonary sling, Left Ventricle to Right Atrial Shunt, total anomalous pulmonary venous return (TAPVR), partial anomalous pulmonary venous return (PAPVR), and transposition of the great vessels. It covers certain peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis and assorted cerebral vascular diseases including migraine. There is hypotension, which can arise from all sorts of other problems. There are a number of different forms of vasculitis, including Churg-Strauss vasculitis, consecutive vasculitis, granulomatous vasculitis of central nervous system, hypersensitivity vasculitis, (called also allergic or leukocytoclastic vasculitis or leukocytoclastic angiitis which arises from hypersensitivity to an antigenic stimulus), hypocomplementemic vasculitis, isolated vasculitis of central nervous system, nodular vasculitis, overlap vasculitis (polyangiitis overlap syndrome), pulmonary vasculitis including Wegener's granulomatosis, rheumatoid vasculitis, segmented hyalinizing vasculitis (livedo vasculitis), Polyarteritis nodosa, and urticarial vasculitis. There are also specific forms of arteritis, including coronary arteritis, equine viral arteritis, giant cell

arteritis (cranial, granulomatous, or temporal arteritis or Horton's disease), infantile arteritis, infectious arteritis, arteritis obliterans (endarteritis obliterans), rheumatic arteritis, syphilitic arteritis, Takayasu's arteritis (aortic arch, or brachiocephalic arteritis or Martorell's syndrome or pulseless disease), tuberculous arteritis, endarteritis obliterans, arteritis umbilicalis, and verminous mesenteric arteritis. There are different forms of Vascular dementia, including multi-infarct dementia (MID), Binswanger's Disease and Arteriosclerotic Dementia. There is a huge collection of other cardiovascular problems, including thymoma (invasive and non-invasive), admixture lesion, left ventricular hypertrophy, tortuous aorta, aortic laceration pulmonary artery sarcoma, aortic regurgitation, pneumomediastinum (Spontaneous and traumatic), middle mediastinal mass, posterior mediastinal mass, Uhl disease, right ventricular hypertrophy, cardiac rhabdomyoma, acute aortic dissection, pericardial cyst, carotid artery bruit, pulmonary embolism, venous angioma, varicose veins and spider veins, congenital heart disease, pericardial effusion, tetralogy of Fallot, coronary artery calcification, endocardial fibroelastosis, fibromuscular dysplasia (FMD), thromboangiitis obliterans (Buerger disease), left or right ventricular volume overload, situs inversus, neonatal heart failure, myocarditis, arteriosclerosis, atherosclerosis, stroke and many others. Cerebrovascular includes different types of Vascular dementia, including multi-infarct dementia (MID), Binswanger's Disease and Arteriosclerotic Dementia, as well as cerebral stroke.

C. Autoimmune. The "autoimmune diseases" are processes which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different

underlying causes. Known autoimmune disorders include multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, alopecia, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behcet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von Meyenburg disease), Retroperitoneal Fibrosis, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), and many more. There are both chronic and acute "autoimmune diseases", most of which lack satisfactory treatment.

D. Peripheral vascular disorders includes Raynaud's disease, acrocyanosis, frost bite, acute arterial occlusion, phlebitis, phlebothrombosis, diabetic gangrene, causalgia, shock and pheochromocytoma; intermittent claudication, digital ulceration, peripheral occlusive vascular disease, diabetic retinopathy and various lower extremity problems, deep-vein thrombosis and thrombophlebitis.

E. Urogenital. Urogenital Diseases covers all diseases of the prostate. Disorders of the prostate covers a broad range of problems. Prostate Cancer is not a single disease or groups of very closely related disorders, but ranges over a very wide variety of cancer types. It embraces various adenocarcinomas of the prostate, including Prostatic Ductal Adenocarcinoma, adenocarcinoma with Paneth-like cells, Clear cell adenocarcinoma, Foamy gland adenocarcinoma, Adenocarcinoma of Cowper's glands, and Atrophic adenocarcinoma. It includes a huge variety of carcinomas, including s mucinous carcinomas of the prostate, Prostatic carcinoma of xanthomatous type, signet ring cell carcinoma of the prostate, neuroendocrine small cell carcinoma of the prostate, and other small cell carcinomas of the prostate, Adenosquamous And Squamous Cell Carcinomas, Basaloid And Adenoid Cystic Carcinoma, Sarcomatoid carcinoma of the prostate, Lymphoepithelioma-like Carcinoma of the prostate, Urothelial (transitional Cell) Carcinoma (which can be primary in the prostate gland or represent secondary spread from the urinary bladder), Basaloid carcinoma, pseudohyperplastic carcinoma, and Primary carcinoma of the Seminal vesicles. There are also assorted sarcomas of the prostate, including Angiosarcoma, Embryonal rhabdomyosarcoma, Stromal sarcoma, Synovial sarcoma, Leiomyosarcoma, and chondrosarcoma of the prostate, which can be primary or secondary to the prostate. Also included is prostatic intraepithelial neoplasia (PIN), Phyllodes Tumor of the Prostate, Primitive peripheral neuroectodermal tumor (PNET) and Malignant fibrous histiocytoma. There are also lymphomas, which are usually secondary, but primary ones include Diffuse Large B-cell Lymphoma.

It covers various forms of prostatitis, including Acute bacterial prostatitis, Chronic bacterial prostatitis, Chronic abacterial prostatitis, eosinophilic prostatitis, Allergic

granulomatous prostatitis, nonspecific granulomatous prostatitis, non-bacterial prostatitis, It covers other prostate disorders, including Malakoplakia, fungal infections, Tuberculosis and bCG-related granulomas. It covers also assorted hyperplasias such as Benign prostatic hyperplasia (BPH), atypical adenomatous hyperplasia, (BCH), Florid basal cell hyperplasia, Clear cell cribriform hyperplasia, and Basal cell hyperplasia, Mesonephric remnants, Mucous gland metaplasia, Post-atrophic hyperplasia , Squamous metaplasia, Urothelial metaplasia, Verumontanum mucosal hyperplasia and Nephrogenic metaplasia. It includes other non-neoplastic conditions of prostate and prostatic urethra, including vascular amyloid deposits, Sclerosing adenosis, blue nevus, assorted Calculi (from phosphate salts of calcium, magnesium, potassium, calcium carbonate or calcium oxalate), Cystadenoma, Ectopic prostate, Endometriosis, Extramedullary hematopoiesis, Ganglioneuroma, various types of infarcts, Inflammatory pseudotumors of the prostate, Leiomyomas, Melanosis, Postoperative spindle cell nodules, Pseudosarcomatous fibromyxoid tumor, Retention cysts, Rhabdomyoma, Signet ring nodule, Urethral polyps, Utricle cysts, and Venous thrombosis. Urogenital Diseases also covers all disorders of the kidney. There are scores and scores of kidney diseases, and these are extremely diverse in nature and origin. There are an assortment of tropical bacterial nephropathies, arising from Salmonellosis, typus, Leprosy, Leptospirosis and others. There is also membranoproliferative glomerulonephritis caused by Hepatitis C, and membranous glomerulonephritis caused by Hepatitis B. There are numerous forms of vasculitis which affect the kidney, such as Polyarteritis nodosa (PAN), Takayasu's disease (Pulseless disease), Kawasaki disease, Temporal arteritis (Giant cell arteritis), Churg-Strauss syndrome, Microscopic Polyarteritis (MPA), Wegener's granulomatosis, Henoch –Schonlein Purpura, Goodpasture's syndrome, Micrtoscopic

polyanglitis, Cryoglobulinemic vasculitis, Lupus vasculitis and others. There are various forms of Amyloidosis: Primary amyloidosis (AL), Secondary amyloidosis (AA), Familial amyloidosis (AF), Senile systemic amyloidosis (AS), and Dialysis amyloidosis (AD). There are an assortment of Acid-Base Disorders including or arising from Alcoholic Ketoacidosis, Chronic Renal Failure, Diabetic Ketoacidosis, Cyanide Poisoning, Glycol Abuse, Lactic Acidosis, Metabolic Acidosis, Metabolic Alkalosis, Methanol Abuse, Respiratory Acidosis, Respiratory Alkalosis and Salicylate Poisoning. There are Fluid and Electrolyte Disturbances i.e. in Calcium, Magnesium, Phosphate, Potassium, Sodium as well as Water Imbalance. There is a heterogeneous collection of polycystic kidney diseases, which are autosomal, and have been linked to three different genes (Autosomal dominant PKD, Autosomal recessive PKD, and Acquired cystic kidney disease (ACKD)). It includes numerous renal tube disorders, including Fanconi's syndrome, hartnup disease, Renal glucosuria, the entire family of Bartter syndromes, Dent's disease, Blue diaper syndrome and many more. There is also nephroblastema, nephroblastoma, nephroblastomatosis, nephrocalcinosis, nephrocele, nephrogenic adenoma, nephrogenic diabetes insipidus, nephromalacia, mesoblastic nephroma, nephromegaly, nephroptosis, nephrosclerosis, nephrotic oedema, renal multicycstic dysplasia, and nephrotuberculosis. There are various forms of diabetic nephropathy and there is sickle cell disease. There are also an assortment of hereditary and congenital glomerular disorders, including Alport's syndrome, benign familiar hematuria, Fabry's disease, nail-patella syndrome, Lecithin-chlolesterol acyl transferase deficiency (an autosomal recessive disorder), Lipoprotein glomerulopathy, nephropathic cystinosis, congenital nephritic syndrome of the Finnish type, and diffuse mesangial sclerosis.

It also covers all disorders of the bladder, including different forms of Bladder Cancer, Urinary Incontinence, Urinary Tract Infection, Cystocele.

It includes all forms of infertility and sexual dysfunction, including Erectile Dysfunction, climacteric disorders, Peyronie's Disease, Vesicoureteral Reflux etc.

F. The scope of "respiratory tract" diseases and disorders covers a vast range of disorders, which vary in their nature, origins, where in the respiratory system they arise, and treatment.

Pharyngitis is infection and inflammation of the throat (including the nasopharynx, uvula, and soft palate)and tonsillitis is of the tonsils. These are caused by a variety of viruses (adenoviruses, influenza viruses, parainfluenza viruses, Epstein-Barr virus, enteroviruses, Herpes simplex virus), mycoplasmas (e.g. Mycoplasma pneumoniae), and bacteria (Group A Beta Hemolytic Streptococci (GABHS), Streptococcus pyogenes, Neisseria Gonorrhea, Hemophilus Influenza Type B) as well as fungal infections, parasitic infections, cigarette smoke, and unknown causes.

The "common cold" is one of the most common respiratory disorders, can be the result of more than 200 different viruses: the rhinoviruses and the coronaviruses cause the majority of colds.

Sinusitis is the arises from the infection of the mucosal lining of one or more of the 4 cavities near the nasal passages (ethmoid, maxillary, frontal, and sphenoid sinuses). It commonly accompanies upper respiratory viral infections which obstruct the opening, but such obstruction can also arise from abnormalities in the structure of the nose, enlarged adenoids, diving/swimming, infections from a tooth, trauma to the nose, and foreign objects that are stuck in the nose. Bacteria, notably Streptococcus pneumonia, Haemophilus

influenza, and Moraxella catarrhalis grown in the trapped secretions. In most cases it requires no treatment, but antibiotics may be given, along with acetaminophen for pain and nosedrops, for relief of symptoms.

Influenza (or flu) is a highly contagious viral respiratory tract infection. Influenza viruses are divided into three types, designated as A, B, and C, which are always mutating. Treatment includes specific antivirals, Relenza (zanamivir); Tamiflu (oseltamivir phosphate); Symmetrel (amantadine), and Flumadine (rimantadine) and the flu vaccine form Flu-mist ™.

Asthma is a chronic, inflammatory lung disease involving recurrent breathing problems. It is characterized by three airway problems: obstruction, inflammation, and hyper-responsiveness. These lead to contraction of airway muscles, mucus production, and swelling in the airways. There are many different asthma triggers.

Acute bronchitis is the inflammation of mucous membranes of the bronchial tubes and is usually caused by infectious agents such as bacteria or viruses. It may also be caused by physical or chemical agents -- dusts, allergens, strong fumes -- and those from chemical cleaning compounds, or tobacco smoke. (Acute asthmatic bronchitis may happen as the result of an asthma attack, or it may be the cause of an asthma attack.) Acute bronchitis is usually a mild, and self-limiting condition, with complete healing and return to function. Most of the treatment is supportive of the symptoms, and may include analgesics, such as acetaminophen for fever and discomfort.

Chronic bronchitis is a long-term inflammation of the bronchi, which results in increased production of mucus, as well as other changes. Chronic bronchitis has no specific organism recognized as the cause of the disease. Cigarette smoking is cited as

the most common contributor to chronic bronchitis, followed by bacterial or viral infections and environmental pollution. Treatment may include bronchodilators for inhaled medications, oxygen supplementation, lung reduction surgery and lung transplantation.

Pulmonary Emphysema is a chronic lung condition in which alveoli (air sacs) may be destroyed, narrowed, collapsed, stretched or over-inflated. Pulmonary emphysema occurs when a breakdown in the chemical balance that protects the lungs against the destruction of the elastic fibers occurs. This can arise from smoking, exposure to air pollution, irritating fumes and a rare, inherited form of the disease, called alpha 1-antitrypsin (AAT)deficiency-related pulmonary emphysema, or early onset pulmonary emphysema. Treatment may include antibiotics for bacterial infections or bronchodilators or other interventions, but these do not treat the underlying disease itself.

Interstitial lung disease, or ILD, (interstitial pulmonary fibrosis) is a term that includes more than 180 chronic lung disorders, which may be chronic, nonmalignant (non-cancerous) and noninfectious. Interstitial lung diseases are named after the tissue between the air sacs of the lungs called the interstitium -- the tissue affected by fibrosis (scarring). The common link between the many forms of ILD is that they all begin with an inflammation. The three main kinds are bronchiolitis - inflammation that involves the bronchioles (small airways); alveolitis - inflammation that involves the alveoli (air sacs); and vasculitis - inflammation that involves the small blood vessels (capillaries). More than 80 percent of interstitial lung diseases are diagnosed as pneumoconiosis, a drug-induced disease, or hypersensitivity pneumonitis. Some other types are idiopathic pulmonary fibrosis, bronchiolitis obliterans, histiocytosis X, chronic eosinophilic pneumonia, granulomatous vasculitis, Goodpasture's syndrome and pulmonary alveolar proteinosis.

The cause of interstitial lung disease is not known, however, a major contributing factor is thought to be inhaling environmental pollutants. Other contributing factors include Sarcoidosis, certain drugs, radiation, connective tissue or collagen diseases and family history. Treatments may include corticosteroids, influenza or pneumococcal pneumonia vaccine but these are of limited effectiveness.

There are many Occupational Lung Diseases, arising from repeated and long-term exposure to certain irritants on the job. These include for example asbestosis, coal worker's pneumoconiosis (caused by inhaling coal dust), silicosis (caused by inhaling free crystalline silica), byssinosis (caused by dust from hemp, flax, and cotton processing, also known as brown lung disease), hypersensitivity pneumonitis (caused by the inhalation of fungus spores from moldy hay, bird droppings, and other organic dusts and occupational asthma (caused by inhaling certain irritants in the workplace, such as dusts, gases, fumes, and vapors).

Pneumonia is an inflammation of the lungs. Lobar pneumonia affects one or more sections (lobes) of the lungs. Bronchial pneumonia (or bronchopneumonia) affects patches throughout both lungs. Bacterial pneumonia is caused by various bacteria notably Streptococcus pneumoniae. Viral pneumonia is caused by viruses (such as respiratory syncytial, parainfluenza, and influenza), Other causes are fungi, mycoplasmas, rickettsias (especially Q fever), Chlamydia, or parasites. It can also occur as a hypersensitivity, or allergic response, to agents such as mold, humidifiers, and animal excreta, and in such a case would be treated with anti-allergic agents. Treatment may include antibiotics for bacterial pneumonia. Antibiotics may also speed recovery from mycoplasma pneumonia and some special cases. There is no clearly effective treatment for viral pneumonia.

Pulmonary hypertension is a lung disorder in which the blood pressure in the pulmonary artery rises far above normal levels. Exact causes of primary pulmonary hypertension remain unknown. Researchers believe the blood vessels are particularly sensitive to certain internal or external factors, and constrict, or narrow, when exposed to these factors. There may be a genetic factor, an immune system factor, or sensitivity to drugs or other chemicals. Treatment may include anticoagulants, diuretics, various drugs to help lower blood pressure in the lungs, and calcium channel blocking drugs and even lung transplantation.

Pulmonary embolism, a severe and life-threatening condition, is the blocking of the pulmonary artery by foreign matter such as a blood clot (thrombus) or pieces of it, fat , air or tumor tissue. Conditions that may contribute to pulmonary embolism include heart disease, chronic obstructive pulmonary diseases (COPD), extended bed rest, surgery, cancer, paralysis, aging, sickle cell disease. The immediate treatment for pulmonary embolism is anticoagulant therapy to dissolve the clot and return blood flow. Oxygen and sedatives may also be used to make the patient comfortable. Surgery to remove the embolism may also be performed.

Pulmonary Sarcoidosis causes small lumps, or granulomas, which generally heal and disappear on their own. However, for those granulomas that do not heal, the tissue can remain inflamed and become scarred, or fibrotic. Pulmonary sarcoidosis can develop into pulmonary fibrosis. Treatment may include the use of corticosteroids.

Tuberculosis (TB) is a chronic bacterial infection that usually infects the lungs. The predominant TB bacterium is Mycobacterium tuberculosis (M. tuberculosis). Treatments employ antibiotics.

Stevens-Johnson syndrome (SJS) is an immune-complex–mediated hypersensitivity disorder caused by many drugs, viral infections, and malignancies and is often of unknown origin. It can trigger Mucosal shedding in the tracheobronchial tree which can lead to respiratory failure.

Lung Cancer usually starts in the lining of the bronchi, but can also begin in other areas of the respiratory system, including the trachea, bronchioles, or alveoli. Nearly all lung cancers are carcinomas. The tumor cells of each type of lung cancer grow and spread differently, and each type requires different treatment. More than 95 percent of lung cancers belong to the group called bronchogenic carcinoma, generally divided into two types: Non small cell lung cancer (Squamous cell carcinoma, also called epidermoid carcinoma, Adenocarcinoma and Large cell carcinomas are the three most important examples), and Small cell lung cancer, sometimes called oat cell cancer. Surgery, radiation therapy, and chemotherapy of many different types may be used in the treatment of lung cancer.

In addition there is Mesothelioma, cancer of the lining of the lung, which causes substantial loss of respiration. It is treated by removal of the lung, and adjuvant therapy.

Atelectasis refers to collapse of the lung, which may be complete or partial. Plugging of a bronchus by various pathologies is a major cause, since gas trapped in the alveoli dissolves in the blood and is carried away. An acute, massive collapse is most often found in patients following an operation, due to both limited respiratory movements in the recovering patient and excess mucus production.

Sleep apnea is a breathing disorder characterized by brief interruptions of breathing during sleep. There are two types: central (occurs when the brain fails to send

the appropriate signals), and obstructive (occurs when air cannot flow into or out of the person's nose or mouth although efforts to breathe continue.) Medications are generally not effective in the treatment of sleep apnea. Therapy may include oxygen administration, behavioral physical or mechanical therapy such as nasal continuous positive airway pressure (CPAP), dental appliances that reposition the lower jaw and the tongue and surgery, such as Uvulopalatopharyngoplasty (UPPP) and surgical reconstruction for deformities of the lower jaw.

Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients. Treatment primarily involves supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

Meconium Aspiration Syndrome is caused by the presence of thick meconium in the distal airways, causing a valvelike mechanism that obstructs air movement. It can occur in a stressed neonate in utero or at the time of delivery. Treatment requires pulmonary support, as well as management of asphyxia-related effects on CNS, cardiovascular system, renal and GI systems, high-frequency ventilation, nitrous oxide, and ECMO.

Spontaneous Pneumothorax symptoms include tachypnea, minimal retractions, grunting, nasal flaring, cyanosis. There will often be diminished air entry on effected side, shifting of cardiac impulse, muffled heart tones. Treatment is supportive, or use of chest tube.

Pink Disease (also known as acrodynia, Erythoedema, Feer's Disease, Swift's Disease) causes respiratory distress, weepy red rash, peeling skin, lethargy, anemia, and other disorders. It is caused by exposure to mercury of babies who are hypersensitive to mercury

Infant respiratory distress syndrome (hyaline membrane disease) is most apparent in premature infants, whose underdeveloped lungs often do not produce enough surfactant. As the afflicted babies exhale, some alveoli tend to collapse due to their low compliance (greater stiffness). Since blood flowing through these alveoli does not become oxygenated, blood leaving the lungs in the pulmonary veins contains less than normal levels of oxygen. One medical solution is to keep the alveoli open by applying positive pressure to the lungs with a respirator (endotracheal intubation, mechanical ventilatory support) and/or metabolic support. Another is to infuse surfactant from animals into the baby's lungs.

Bronchiectasis is a chronic, abnormal dilation of the bronchi. Pockets form in the air tubes of the lung and become sites for infection. Often the cause is an infection, such as severe pneumonia. But other irritations of the bronchi, such as might occur in cystic fibrosis, may be responsible.

Whooping Cough is caused by Bordetella pertussis which colonizes the cilia of the mammalian respiratory epithelium. It is treated with antibiotics.

Wegener's Granulomatosis is a disease that usually begins as a localized granulomatous inflammation of upper or lower respiratory tract mucosa and may progress into generalized necrotizing granulomatous vasculitis and glomerulonephritis. The cause is unknown. Although the disease resembles an infectious process, no causative agent has been isolated. Treatment is with immunosuppressive cytotoxic drugs.

Rhinitis is a reaction that occurs in the eyes, nose and throat when airborne irritants (allergens) trigger the release of histamine. Histamine causes inflammation and fluid production in the fragile linings of nasal passages, sinuses, and eyelids. The two categories of rhinitis are allergic rhinitis (seasonal and perennial) and nonallergic Rhinitis (including eosinophilic, rhinitis medicamentosa, vasomotor Rhinitis, neutrophilic rhinosinusitis, and others), which come from fumes, odors, temperature or atmospheric changes, smoke, etc. Treatments for nonallergic rhinitis include oral medications, inhaled medications, immunotherapy, and surgery for some conditions.

Croup is a contagious viral infection of the upper and lower airways is known as croup. Para-influenza, the measles virus, respiratory syncytial virus or an influenza virus are the normal causes. Treatment is only supportive, including humidifiers, cool mist vaporizers or an ultrasonic nebulizer.

Primary Pulmonary Hypertension is an extremely complex disorder which may lead to congestive heart failure and respiratory failure. PPH is likely caused by some type of infection that arrives in the pulmonary vascular bed in genetically susceptible persons. There are a limited number of drugs available, notably Flolan ® and Remodulin.

Vocal Cord Dysfunction (VCD) (also called Episodic Laryngeal Dyskinesia (ELD), Paradoxical Vocal Cord Motion (PVCM), and Nonorganic upper airway obstruction), is a condition of "throat" (actually, larynx) closure &/or choking sensation that can cause sudden, severe episodes of breathing difficulty, sometimes with wheezing &/or stridor. A wide number of sources have been identified, including infectious sources (e.g. Laryngeal papillomatosis, Infectious mononucleosis, and Tetanus); Traumatic (e.g. Post-intubation injury, Facial fractures and Laryngotracheal trauma); neurologic (e.g. Myasthenia gravis,

Meige's syndrome, Bulbar palsy), Cancerous (Carcinoma of the thyroid, esophagus, larynx, or pharynx), Hereditary angioneurotic edema, Acquired subglottic Stenosis and foreign body aspiration. Acute treatment includes inhaled mixture of 70%-80% Helium/30%-20% Oxygen; CPAP (Continuous positive airway pressure); IPPV (Intermittent positive pressure ventilation) and Benzodiazepines. Long term treatment includes Speech therapy, Biofeedback training, supportive psychotherapy, and hypnotherapy.

Laryngospasm involves inappropriate reflex closure of laryngeal structures at three levels: the true vocal cords, false vocal cords, and the supraglottic folds, and can result in pulmonary edema. It can be caused by general anesthesia, metabolic abnormalities such as hypo-calcemia caused by hypo-parathyroidism and by occult gastro-esophageal reflux (GER). It requires emergency treatment to restore air supply.

Primary ciliary dyskinesia is a heterogeneous group of inherited disorders characterized by a structural and generalized abnormality of cilia which renders them immotile or dysmotile. Mucus clearance from the respiratory tract is impaired, causing chronic upper and lower airway disease. Treatment of PCD is symptomatic, and is directed against respiratory tract complications. Antimicrobials are use to suppress bacterial colonization and recurrent infection; bronchodilators are useful in curbing airway reactivity. Physiotherapy and postural drainage are often important adjuncts.

Recurrant repiratory infections can arise from many sources such as metabolic disorders e.g. Mucopolysaccharidosis I (the cause of Hurler- Scheie syndrome).

The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for respiratory diseases. It establishes that it is not reasonable to any agent to be able to treat such diseases generally.

G. The claim also mentions "complications" from diabetes, a very diverse set of disorders. These diabetic complications include intercapillary glomerulosclerosis, various forms of retinopathy and assorted neuropathies, coronary heart disease, and many other disorders. It includes peripheral vascular disease (PVD), such as Atherosclerosis is common in patients with diabetes, and increased incidences of microangiopathy and macroangiopathy, which can cause an accelerated form of atherosclerosis that affects e.g. the coronary, carotid, aortic, iliac, femoral, popliteal, tibial, and peroneal vessels. There is also diabetic neuropathis, including for example, distal symmetric sensorimotor polyneuropathy, focal and multifocal neuropathies, entrapment neuropathy, autonomic neuropathy, and sensorimotor polyneuropathy. There are an assortment of diabetic foot conditions generally arising from ensory neuropathy. These include ulceration, impaired neutrophils, fibroblasts, and leukocyte activity infection leading not defective or incomplete wound healing, foot deformities (e.g. hammer and claw toes and depression of the metatarsal heads), Charcot neuroarthropathy, osteoarthritis, and ultimately foot amputation.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is largely worthless. The daily dosage range information provided on page 85, line 15 is a 100,000 fold range, generally useless. Further, it is completely generic. That is, it is the same dosage for all disorders listed in the specification, which is a very substantial range of disorders.

(4) State of the Prior Art: The claimed compounds are amino-xanthines with a particular substitution pattern. So far as the examiner is aware, amino-xanthines have not been successfully used as anticancer agents, for kidney or prostate disorders, for autoimmune disorders, etc.

(5) Working Examples: There are none of any kind. There is data showing that the compounds are PDE V inhibitors.

(6) Skill of those in the art:

I. Cancer. The prior art knows that there never has been a compound capable of treating cancer generally. There are compounds that treat a modest range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect just a single organ are often not generally treatable. As an example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. That is, there is no one compound that can treat these generally, or even most of them, nor is there any reason to think that

there could be such a compound. Since it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. The skill thus depends on the particular cancer involved. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available. As an example, one skilled in the art knows that chemotherapy of brain tumors is especially difficult. This is because 1) the blood-brain barrier, which is often intact in parts or all of a brain tumor, will block out many drugs, as it is the purpose of the blood-brain barrier to protect the brain from alien chemicals, and 2) CNS tumors are characterized by marked heterogeneity, which greatly decreases vulnerability to chemotherapy. As a result, many categories of CNS tumors simply have no chemotherapy available. These include, generally, hemangiomas and hemangioblastomas, low grade gliomas, meningiomas, craniopharyngiomas, acoustic neuromas, pituitary adenomas, optic nerve gliomas, glomus jugulare tumors and chordomas, to name just some. The majority of common cancers do not respond to chemotherapy.

II. The skill level in the art of pharmacological treatment of cardiovascular disorders varies with the disorder. In some areas such as hypertension it is relatively high. But in the great majority of cases it is very low as the disorders cannot be treated with pharmaceuticals. There are a wide variety of causes. For example, just for the Vascular dementias, these can be caused when caused when small arteries in the brain burst (cerebral hemorrhage), or arteries are blocked by plaque formation or clots (thrombosis or embolism), or there is insufficient blood flow to parts of the brain (ischemia). Stroke is the most common cause, but it can arise from auto-immune inflammatory diseases of the arteries such as Systemic

Lupus Erythermotsis and Temporal Arteritis; sometimes the cause is completely unknown. A huge assortment of inflammatory processes can result in various forms of vasculitis. Genetic defects and developmental problems are responsible for many types of structural problems. Metabolic disorders such as Mucopolysaccharidosis I (the cause of Hurler- Scheie syndrome) can cause vascular deposits of mucopolysaccharides with arteriosclerosis, heart murmur, and aortic regurgitation. The vast majority are treated either by surgical means or cannot be treated at all, leaving only general management of symptoms.

III. Autoimmune. One of ordinary skill in the art knows there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and

causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE.

Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found. Many autoimmune disorders are completely intractable.

IV. The great majority of prostate cancers are not treatable with pharmaceuticals. This is also true for genetic and for structural problems in the kidney and for structural problems of the bladder.

V. The skill level in the treatment of respiratory disorders varies greatly. Some disorders such as ARDS and viral infections other than influenza and RSV (e.g. rhinoviruses and the coronaviruses) generally cannot be treated with pharmaceuticals.

VI. Much the same is true for urogenital disorders. For example PKD cannot itself be treated. Drugs can be given for conditions secondary to PKD, e.g. drugs to control high blood pressure, and antibiotics to control urinary tract infections and pain medication, but these do not treat the PKD itself. There are large number of kidney diseases which are genetic in origin and are by and large untreatable per se.

VII. Polycystic ovary syndrome (PCOS or POS or Stein-Leventhal syndrome) is a complex endocrine disorder associated with anovulation and an excess of androgens in the blood. The disorder is characterized by the formation of cysts in the ovaries. Treatment is done by inducing ovulation, using an insulin sensitizing drug such as Metformin, Pioglitazone or Rosiglitazone, or fertility drugs such as Clomiphene citrate. Other drugs are employed, such as Progestins, Oral Contraceptives and GnRH agonists to suppress LH, or Anti-Androgens such as spironolactone flutamide and finasteride, to ameliorate certain symptoms, but do not treat the disorder itself.

VIII. In general, these compounds are disclosed to be PDE V inhibitors. Such compounds can elevate cGMP leves and can be used to treat erectile dysfunction, but have not been

established as effective for any other purpose. And of course, the above disorders are not limited to those which have any connection to PDE V.

(7) The quantity of experimentation needed: Given the fact that historically the development of new e.g. cancer or autoimmune drugs has been difficult and time consuming, and especially in view of factors 1, 4 and 6, the quantity of experimentation needed is expected to be great.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12, 22-29, 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-11 of U.S. Patent No. 6821978. Although the conflicting claims are not identical, they are not patentably distinct from each other because of overlap.

The claims in this case are drawn to R4 as optionally substituted heterocycloalkyl, e.g. tetrahydropyranyl as see in e.g. claim 42. However, the parent case also has tetrahydropyranyl in its claims 10-11. It is not at all clear why that material is present in the patent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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5/25/05